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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,873	05/08/2001	Rolf F. Kletzien	28341/00233.NCP	4967

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	**PAPER NUMBER**
1652	9

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,873	KLETZIEN ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *6 and 9-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 7, 8* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 May 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-49 are at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, and sequence R, SEQ ID NO: 76 or SEQ ID NO: 79, Claims 1-5, 7 and 8, in Paper No. 8 is acknowledged.

The traversal is on the ground(s) that the groups of inventions delineated (i.e. Groups I-VIII) are related and thus not independent and distinct and that coexamination of the additional groups would not require an additional burden of search. This is not found persuasive because while 35 § U.S.C. 121 states that restriction may be required between independent and distinct inventions as delineated in MPEP 802.01 this language was intended to codify the existing practice of division at the time of the 1952 Patent Act which unquestionably included the division of dependent (or related) inventions. As such restriction is proper if two or more claimed inventions are either independent or distinct. see MPEP 803. Furthermore coexamination of each of the additional groups would require search of subclasses unnecessary for the examination of the elected claims. For example, the search for the invention of Group II would include search of subclass, the search for the invention of Group III would include search of subclass 536/23.2, the search for the invention of Group III would include search of subclass 530/387.1, the search for the invention of Group IV and V would include search of subclass 435/69.1, the search for the invention of Group VI would include search of subclass 514/789, the search for the invention of Group VII would

include search of subclass 424/94.65, and the search for the invention of Group VIII would include search of subclass 514/44. Therefore, coexamination of each of these additional inventions would require a serious additional burden of search based on the different classes necessary to examine the additional inventions.

Applicants further traverse the restriction of the different polynucleotide and polypeptide sequences listed as A-U and V-A' on the basis that Groups A-U are isoforms of human caspase 12 and the polypeptides of Groups V-A' are peptides of human Caspase-12, and thus the specification as filed discloses the relationship among these molecules and they are further connected in design, operation and effect. This argument is not found persuasive because while it is acknowledged the different molecules are related they are still structurally different molecules which are not disclosed as capable of use together and they have different modes of operation, different functions or different effects. Applicants in their traversal have pointed out that the different molecules are connected in design, operation and effect. As above, while it is acknowledged that the different molecules do share some common design, operation and effect, these are not identical for any of the different molecules. As stated previously, where structural identity is required, the different sequences have different effects. Thus while the different inventions are not as distantly related as a shoe and a locomotive, they are drawn to structurally different molecules which are independent and distinct.

Applicants argument that those claims reciting the subject matter of Groups A-A' are Markush-style claims is not found persuasive because as stated in M.P.E.P. 802.02

if the subject matter in the claim lacks unity of invention, restriction may be proper. As applicants have not disclosed that the different inventions share common utility or a substantial structural feature disclosed as being essential to that utility.

Applicants traverse that the invention of Group I and Groups IV, V and VI(VII) are distinct on the basis that the process of using the polypeptide of Group I to synthesize antibodies is not materially different from the processes of claims of Groups IV-VI, because antibodies can be used in these processes as controls. This is not found persuasive because while these different processes may be combined, they are materially different processes.

Applicants traverse the distinctness of Groups II and VIII on the same basis as Groups I and Groups IV, V and VII above. This is not found persuasive for the same reasons as above.

Applicants traverse that the invention of Group II and III and Groups IV-VII are related in as much as the polynucleotides of Group II are used to produce the polypeptides, which are then used in the methods of Groups IV-VII. This is not found persuasive because while these different products may be related in some sense to the polypeptides of Group I, they are not used by the methods of Groups IV-VII and are therefore distinct.

Applicants traverse that the invention of Group I and Group VI are distinct on the basis that the polypeptide of Group I is used to identify the inhibitor used in the treatment. This is not found persuasive because while the polypeptide is related to the

inhibitor in some sense, it remains that it is not used in the process of use of the inhibitor and the two inventions are distinct.

Applicants traverse that the invention of Group I and III and the invention of Group VII are related in a similar fashion as the above argument of the distinctness of Group I and Groups IV, V and VII. As above, this is not found persuasive because while the polypeptide and antibody are related to the polynucleotide in some sense, it remains that they are not used in the process of use of the polynucleotide and the inventions are thus distinct.

Applicants traversal of the distinctness of Groups V-VIII on the basis as the above arguments, that the products of one method can be used for a different method and the products of the second method can be used in a different method still is not found persuasive, as above. The methods of Groups V-VIII are independent as they comprise different steps, utilize different products and produce different results and would require different searches for their proper examination, the combination of which would place an undue burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6 and 9-49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8.

Priority

Applicants claim of the benefit of U.S. Provisional application 60/203,162, filed May 9, 2000, is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosures, Paper No. 6, filed 6/14/2002, is acknowledged. Those references considered have been initialed.

Drawings

The drawings filed on 5/8/2001 are objected to for the reasons stated on the enclosed form PTO-948.

Figure 1 recites a number of times "SEQ ID NO:____" This blank should be filled in or deleted if the SEQ ID NO's listed in the description is accurate.

Note, applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Specification

The disclosure is objected to because of the following informalities:

As discussed above, Figure 1 recites a number of times "SEQ ID NO:____" This blank should be filled in or deleted if the SEQ ID NO's listed in the description is accurate.

Appropriate correction is required.

Claim Objections

Claims 1-5, 7 and 8 are objected to because of the following informalities:

Claims 1-5, 7 and 8 each recite non-elected subject matter.

Claim 4 is dependent on rejected claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent". While page 21 of the specification describes some conditions which are intended to be stringent, there is nothing to suggest that other conditions would not also be included within the scope of

this term and in the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a polynucleotide of SEQ ID NO: 76, a sequence must be to be included within the scope of these claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5, 7 and 8 are directed to all possible caspase polypeptides comprising an amino acid sequence that is at least about 98% identical to 30 contiguous amino acids of SEQ ID NO: 79 and fusion polypeptides comprising said caspase polypeptide (claims 1, 5 or 8), wherein said polypeptide is encoded by a polynucleotide that hybridizes under stringent conditions to SEQ ID NO: 76, or the non-coding strand thereof (claim 7) and those caspase polypeptides comprising at least about 20 (claim 2) or 40 (claim 3) contiguous amino acids of SEQ ID NO: 79, wherein said polypeptide comprises at least one subunit of human caspase-12 (claim 5). The specification, however, only provides a single representative species comprising SEQ ID NO: 79 encompassed by these claims. There is no disclosure of any particular

structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these polypeptides by any identifying structural characteristics or properties other than the those limitations recited in claims 1-3, 5, 7, for which no predictability is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-3, 5, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a caspase polypeptide comprising the amino acid sequence of SEQ ID NO: 79, does not reasonably provide enablement for any caspase polypeptide comprising an amino acid sequence at least 98% identical to 30 contiguous amino acids of SEQ ID NO: 79. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3, 5, 7 and 8 are so broad as to encompass any caspase polypeptide comprising an amino acid sequence that is at least about 98% identical to 30 contiguous amino acids of SEQ ID NO: 79 and fusion polypeptides comprising said caspase polypeptide (claims 1, 5 or 8), wherein said polypeptide is encoded by a polynucleotide that hybridizes under stringent conditions to SEQ ID NO: 76, or the non-coding strand thereof (claim 7) and any caspase polypeptide comprising at least about 20 (claim 2) or 40 (claim 3) contiguous amino acids of SEQ ID NO: 79, wherein said polypeptide comprises at least one subunit of human caspase-12 (claim 5).

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims, including all caspase polypeptides comprising at least 20 contiguous amino acids of SEQ ID NO: 79 and variants thereof. The claims rejected under this section of U.S.C. 112, first paragraph, place minor structural limits on the claimed polypeptides. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to

modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those caspase polypeptides comprising the amino acid sequence of SEQ ID NO: 79.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any caspase polypeptide having the claimed relationship to SEQ ID NO: 79, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting caspase activity; (B) the general tolerance of the claimed caspase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a caspase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain caspase activity and the fact that the relationship between

the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of a caspase comprising the amino acid sequence of SEQ ID NO: 79. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

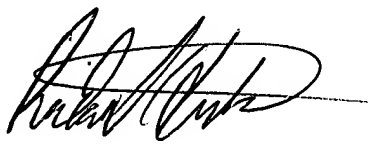
Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
December 27, 2002